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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

2-13-84

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM
~~DATE:~~ ~~undated~~

TO: Richard Mountfort, PM#23
Registration Division (TS-767)

FROM: Gary J. Burin, Toxicologist Gary J Burin
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Hazard Evaluation Division (TS-769)

THRU: Laurence D. Chitlik, Section Head LDC 2/13/84
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SUBJECT: Proposed Metolachlor Lab Audit and Memo of January 26, 1984 from Dexter Goldman Tox. Chem. #188DD

Background Information:

In my memo of December 14, 1983 (attached), I recommended a lab audit be considered to resolve the issue of conflicting tumor incidences reported by the testing laboratory in a preliminary report compared to the Final Report of the study. Aside from the tumor incidence issue, I had no problems with the study conduct or reporting that would warrant a lab audit of other aspects of the study.

I have recently received a memo from Dexter Goldman, Head, Data Integrity Program (dated January 26, 1984, attached) which suggested that a lab audit may not be the most appropriate way of resolving the issues raised in the HED review. Dr. Goldman suggests that an "independent and blind review of rat liver slides with a new pathology narrative" be pursued rather than a lab audit.

Discussion/Recommendation:

From the standpoint of completing the hazard evaluation and risk assessment for metolachlor, Dr. Goldman's recommendation is completely acceptable. However, a lab audit may possibly resolve

the issue without having to reread the slides. Depending upon the results of the lab audit, a decision would then have to be made as to whether or not a rereading of the slides would be necessary.

I would also like to clarify several issues raised in Dr. Goldman's memo.

1. The results presented in the preliminary report were not only the results of diagnoses of interim sacrifice animals but were the total for all animals (moribund sacrifice, spontaneous deaths and terminal sacrifices). The basis for conducting the rediagnoses remains unclear and whether or not the rediagnoses was done by the same or a different pathologist remains unknown. In other words, was there a second pathology report not submitted to the Agency?

2. Regarding the combining of neoplastic nodules with hepatocellular carcinomas - this was done after consultation with the Toxicology Branch pathologist and is consistent with the recommendation of National Academy of Sciences (see "Histologic Typing of Liver Tumors of the Rat" JNCI, Vol. 64, No. 1, 1980, p. 185). It is not relevant to the question of whether or not to conduct a lab audit but is relevant only to the determination of oncogenic potential. That determination is further discussed in #3, below.

3. The repeat mouse study has not yet been determined to be negative. Rather, it has not yet been reviewed. The initial mouse study was conducted at IBT and although negative with respect to oncogenicity contained deficiencies which resulted in an agreement with the registrant to repeat of the study. The initial chronic rat study (also conducted at IBT), using the same strain and dose levels as that of the study for which an audit has been suggested, was positive with respect to oncogenicity with a liver tumor incidence similar to that reported in the preliminary report for the repeat study.

Finally, I feel it necessary to expand upon the basis for my original recommendation for a laboratory audit. It seems that there is at least the appearance of a possible problem in the reporting of this study. In cases such as this, it seems appropriate to refer the issue to the laboratory audit program. Based upon resources, priorities and the gravity of the problem the lab audit program can then recommend the most appropriate course of action. Whichever course of action is eventually chosen, I would hope that the issue can be resolved as expediously as possible.

cc: M.Conlon
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A.Rispin
J.McCann
D.Goldman